

each reference discloses compositions for the treatment of cartilage damage, it would be obvious to combine them. Applicants respectfully traverse the rejection.

US 5,972,880 to Pelletier

Pelletier '880 discloses that IL-1 contributes to both reduce anabolic activity and enhance catabolic effects (Col. 2, lines 20-21), and teaches the administration of IL-1 receptor antagonist (IL-1ra). However, Pelletier '880 does not teach or suggest combining this agent with a growth factor or other anabolic promoting agent. Rather, Pelletier '880 specifically teaches away from the claimed methods of locally delivering combinations of a catabolic inhibitor and an anabolic agent. Applicants respectfully direct the Examiner's attention to the same passage of Pelletier '880 cited in the Office Action, Column 3, line 63 - Column 4, line 20. In this passage, Pelletier et al. discuss the formation of osteophytes, which are bony spurs or out growths often associated with pain in arthritic conditions such as osteoarthritis. Pelletier et al. disclose that the administration of IL-1ra in an *in vivo* model results in a reduction of incidence and size of osteophytes, and conclude "it is conceivable that the increase in the local synthesis of growth factors or proinflammatory cytokines by the inflamed synovium may be an important factor in osteophyte formation." Thus Pelletier et al. teach (1) that the catabolic inhibitor IL-1ra demonstrated therapeutic effect by reducing osteophyte production and (2) an increase in growth factors may cause osteophyte formation. Pelletier et al. certainly do not teach to co-administer a growth factor, but do suggest that growth factors may be deleterious, thereby teaching away from the present invention. Pelletier et al. do not discuss beneficial effects of growth factors in arthritic joints.

US 5,206,023 to Hunziker

In contrast, Hunziker '023 takes the opposite effect, disclosing the use of anabolic agents such as TGF- β , but does not disclose the use of inhibitors of cartilage catabolism. As noted in

the prior response, Hunziker '023 does disclose at Column 7, lines 62-65 the use of TNF- α and TNF- β , which are actually pro-inflammatory agents, rather than anti-catabolic antagonists or inhibitors of TNF- α . Thus, Hunziker '023 teaches away from the use of catabolic inhibitors and the present invention.

No *Prima Facie* Case of Obviousness

Neither Pelletier '880, which discloses catabolic inhibitors but teaches away from anabolic chondroprotective agents, nor Hunziker '023, which discloses anabolic agents but teaches away from inhibitors of cartilage catabolism, provides a reason for combining anabolic chondroprotective agents with inhibitors of cartilage catabolism. Rather, these references address two separate prior art approaches, and are consistent with a larger body of art of record which follows either one approach or the other, with a long standing failure to recognize that the approaches should be combined. Applicants respectfully submit that no *prima facie* case of obviousness has been established.

Previously Submitted Evidence of Nonobviousness

Even if one assumes a *prima facie* case of obviousness, which Applicants submit has not been demonstrated here, it is again noted that the applicants have submitted an overwhelming collection of data on the advantages and unexpected results of the present invention, both in the data disclosed in the declaration of Dr. Moore submitted with the prior amendment of November 6, 2006, and also in the non-prior art references providing additional data in support of the invention (publications by Studer et al.) previously submitted. All together, this collection of evidence clearly overcomes any arguable *prima facie* case of obviousness.

Request for Allowance

Applicants respectfully request reconsideration and allowance of Claims 38-51, 53, 56-60 and 73-81, which are submitted to be in condition for allowance. The undersigned attorney would welcome a call to discuss any remaining issues.

Respectfully Submitted,

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Date

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